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Washington Prescription Drug Program
Administered by the Washington State Health Care Authority
A member of the Northwest Prescription Drug Consortium

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Ophthalmic Prostaglandins Review

Background

- Ophthalmic Prostaglandins are Indicated for the treatment of glaucoma and eyelash growth

- **4 agents available:**
  - latanoprost (Xalatan) *generic
  - travoprost (Travatan Z)
  - tafluprost (Zioptan)
  - bimatoprost (Lumigan, Latisse)

- These drugs are dosed once a day, usually at night.

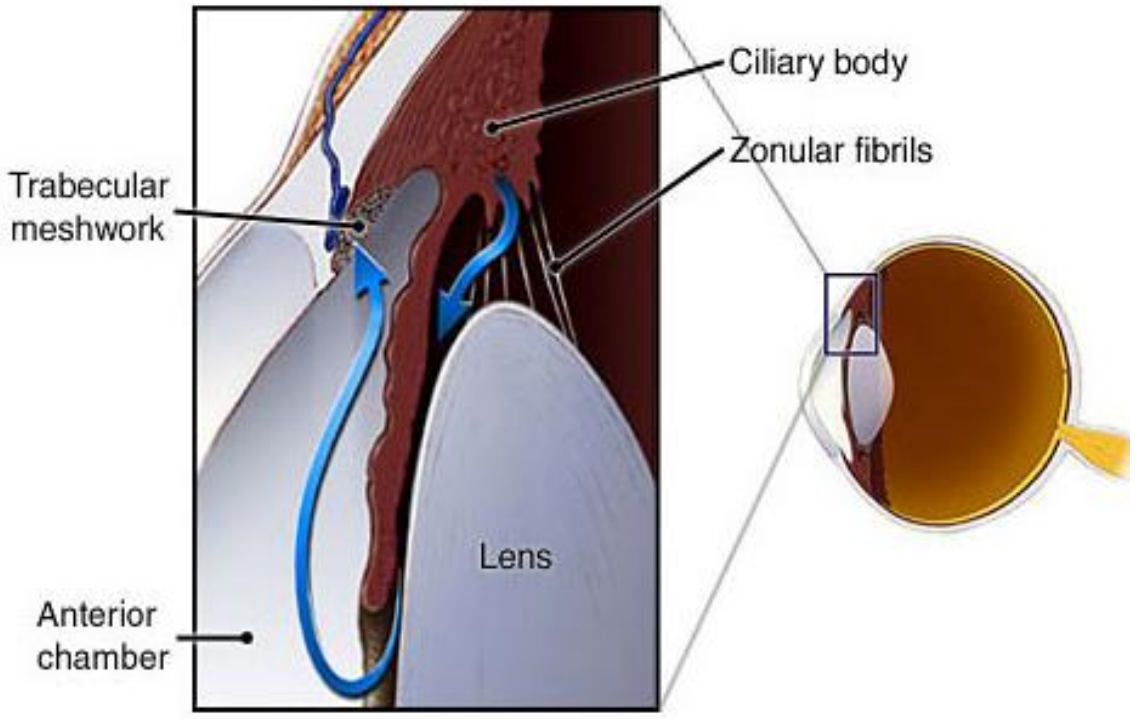
Background

- Ophthalmic Prostaglandins are Indicated for the treatment of open angle glaucoma and eyelash growth

- Lower intraocular pressure (IOP) by increasing the aqueous outflow through the trabecular meshwork.

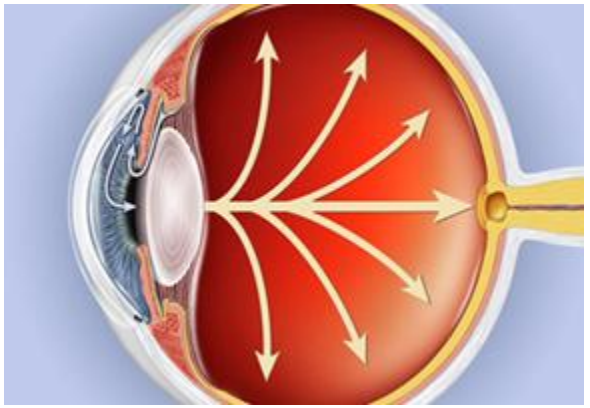
4 agents available:

- travoprost (Travatan Z)
- tafluprost (Zioptan)
- latanoprost (Xalatan)
- bimatoprost (Lumigan, Latisse)



Glaucoma

- Incidence: >2 million Americans, only half of patients with glaucoma know they have it.
- Accounts for 9% to 12% of all cases of blindness in the U.S.
- Progressive optic neuropathy that is often associated with increased intraocular pressure (IOP). Increased IOP is the only disease-related symptom that can be treated.
- Currently, ophthalmic prostaglandins are first line pharmacotherapy for the treatment of glaucoma.
- Drugs used in the treatment of glaucoma:
  - Prostaglandins Analogs
  - Cholinergic Agonists
  - Alpha 2 Agonists
  - Beta-Blockers
  - Carbonic Anhydrase Inhibitors



FDA Approvals

December 2008: bimatoprost 0.03% (Latisse), approved for the treatment of hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness.

June 2010: Travatan (travoprost) 0.004% with the preservative, benzalkonium chloride (BAK) discontinued. Travatan Z (travoprost) 0.004%, to be promoted in Travatan's place.

August 2010: bimatoprost 0.03% (Lumigan), approved for the treatment of elevated intraocular pressure due to glaucoma or ocular hypertension.

February 2012: tafluprost 0.0015% (Zioptan) approved for open angle glaucoma and ocular hypertension. It is the first and only preservative-free prostaglandin analogue.

Clinical Efficacy

Ophthalmic prostaglandins typically lower IOP by 25-30% and stabilize it at a lower level throughout the day and night

Meta analysis

Van der Valk, et. al.

- 27 randomized controlled trials, monotherapy for open angle glaucoma or ocular hypertension.
- Findings: prostaglandin analogues (bimatoprost, latanoprost, travoprost) and timolol most effective.
- Reduction in peak IOP: bimatoprost (33%), latanoprost (31%), travoprost (31%) and timolol (27%).
- Reduction in trough IOP: travoprost (31%), bimatoprost (28%), latanoprost (28%) and timolol (26%).
- No statistical Analysis was provided

Clinical Efficacy

Meta analysis (continued)

Denis, et. al.

- 9 randomized trials, 1318 patients.
- Findings: bimatoprost and travoprost decreased IOP more than latanoprost (-0.98 mmHg and -1.04 mmHg respectively).
- This difference was significant for travoprost only (p = 0.04).

Li, et. al.

- 12 randomized controlled studies of 2 weeks to 12 months (included 6 studies from Denis' meta analysis).
- Findings: travoprost decreased IOP to a greater extent than timolol (p=0.00001), but was not statistically different than bimatoprost or latanoprost (p = 0.8 and 0.07, respectively).
- Travoprost caused significantly more ocular hyperemia and eyelash changes than timolol or latanoprost and was equivalent to bimatoprost for these events

Clinical Efficacy: tafluprost

Zioptan

- In clinical studies, up to 24 months in duration, Zioptan dosed once daily reduced IOP at 3 and 6 months of 6 – 8 mmHg and 5 – 8 mmHg, respectively.
- Long term trial of 52 weeks. 351 patients with open angle glaucoma (including normotensive) or ocular hypertension. Tafluprost lowered IOP within the range of 4.9-5.7 mmHg throughout the 52-week study period.
- Normotensive glaucoma: 94 patients studied in a randomized, masked, comparative study (comparator was placebo). Tafluprost lowered IOP by 4.0 mmHg (95% confidence interval: 3.5 to 4.5 mmHg). This was significantly greater than placebo.

Clinical Efficacy: Comparative Trials

tafluprost vs latanoprost-noninferiority trial

- Randomized, single-blind comparative study, 109 patients with primary open angle glaucoma or ocular hypertension for 4 weeks
  - Tafluprost and latanoprost lowered IOP by 6.6 ± 2.5 mmHg (27.6 ± 9.6%) and 6.2 ± 2.5 mmHg (25.9 ± 9.7%), respectively
  - Percentage of patients showing a reduction of 20% or more in IOP was 80.4% for tafluprost vs 70.6% for latanoprost.
  - Incidence of AEs did not differ between groups. (40.0% tafluprost and 48.1% latanoprost, *P* = 0.443, Fisher's exact test).
  - The most common adverse reaction was conjunctival hyperemia (16.4%, n = 55), which was higher than that of latanoprost (13.0%, n = 54), but not significant
- tafluprost versus latanoprost, noninferiority was also demonstrated by ANOVA (and almost by ANCOVA) in a phase III, 24-month study in patients with open-angle glaucoma or ocular hypertension

Clinical Efficacy: Comparative Trials

bimatoprost vs travoprost

Cantor: N=157; IOP 21-34 mmHg; 3 and 6 months

- Bimatoprost significantly lowered IOP vs travoprost at 9AM ($p<0.014$) but not at 1pm and 4pm.
- Both products significantly lowered IOP compared to baseline at all time points. ($p<0.001$).
- 64.5% of patients taking bimatoprost had an IOP reduction of $\geq$ 25% vs. 39.5% of travoprost patients ($p=0.002$).
- No significant difference in side effect incidence between groups.

Noecker: N=94; African Americans; IOP 22-34; 3 months

- No significant difference in mean IOP lowering between groups was seen (p value not provided).
- Both bimatoprost and travoprost showed significant IOP lowering compared to baseline ($p<0.001$
- No significant difference in number of patients achieving 20, 25, 30 or 40% reduction in IOP between groups.
- No significant difference in side effect incidence between groups.

Clinical Efficacy: Comparative Trials

latanoprost/timolol (0.005%/0.5%) vs travoprost

Franks WA et al. (2006): N= 106; IOP 22-36; 6 weeks

- No significant differences in IOP lowering effects were seen between treatment groups at any time point (9AM or 5PM).
- The average reduction in IOP was 7 mm Hg with travoprost and 6.8 mm Hg with latanoprost/timolol.
- There were no significant differences in side effects between the two treatment groups.
- 9.3% of travoprost and 1.8% of the fixed combination therapy patients reported ocular hyperemia while 5.6% of travoprost and 1.8% of combination therapy patients reported foreign body sensations.
- There were no significant differences in side effects between the two treatment groups.

Clinical Safety

- **AE's associated with long-term use of all ophthalmic prostaglandins:**
  - conjunctival hyperemia
  - darkening of the iris
  - increase in length and number of eyelashes
  - increase in periorbital (eyelid) skin pigmentation.
  - iris pigment changes, (permanent)
- **Localized AE's:**
  - local irritation
  - itching
  - dryness and blurred vision
  - uveitis or cystoid macular edema
- **Systemic effects are rare**

Conclusion

- Most commonly used drug class for the treatment of glaucoma. Considered to be a first line agent as monotherapy.
- Ophthalmic prostaglandin agents are considered to be equally efficacious, lowering IOP by 25-30%
- Bimatoprost may decrease IOP slightly more than latanoprost and travoprost, however the clinical significance of this difference is not clear
- Side effects such as hyperemia, ocular pruritus, and eyelash growth are reported to occur more often with bimatoprost

Questions?